III. REMARKS

A. Status of the Claims:

Claims 1-30 and 87-94 are currently under examination. Claims 31-86 have previously been withdrawn from consideration. Claims 20 and 22 have been amended to consistently recite the term heterodimerization polypeptide instead of sequence. The amendments do not alter the scope of the respective claims. Claim 94 has been amended for the reasons stated in the remark section. No new matter is added.

Upon allowance of the pending claims 1-30 and 87-94, the Examiner is authorized to cancel claims 31-86 drawn to nonelected subject matters.

B. Examiner Interview:

Applicants' attorney greatly appreciates the courtesy that was extended by the Examiner during the telephonic interview conducted on March 25, 2004. During the interview, the rejections under 35 U.S.C. §103(a) and 35 U.S.C. §112 first paragraph were discussed. The Examiner has indicated that the arguments delineated below would be persuasive in overcoming the rejections raised in the Final Office Action.

C. Claim rejections:

1. 35 U.S.C. §103(a)

Claims 1-30 and 87-93 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over the primary reference Glockshuber *et al.* (Biochemistry 29:1362-1367, 1990), in combination of the following secondary references: Pack *et al.* (Biochemistry 31:1579-1584, 1992), Arndt *et al.* (J. Mol. Biol. 295:627-639, 2000), Queen *et al.* (U.S. Patent 5,693,762), and Kammerer *et al.* (Biochemistry 38:13263-69, 1999). Applicants respectfully traverse this rejection for the reasons stated below.

The primary reference by Glockshuber *et al.* does not provide the motivation to design the claimed antigen-binding units

In the Final Office Action, the Office has opined that "*While it is true that Glockshuber's methods to stabilize the Fv fragment have some limitations, this is motivation to use the coiled-coils for stabilization to obtain better molecules.*"

Applicants respectfully point out that the Glockshuber *et al.* does not describe or even suggest any drawbacks of the three strategies employed to stabilize the Fv fragment, which allegedly would have motivated one of ordinary skill in the art to derive the claimed antigen-binding units. Glockshuber *et al.* reports great success with their three stabilization strategies namely, cross-linking, the use of intermolecular disulfide bond, and the construction of single chain Fv fragment that is stabilized by glycine linker. In the abstract of Glockshuber *et al.*, it is described that all three strategies yield Fv fragments having *"binding affinities nearly identical with that of the whole antibody independent of protein concentration and are significantly (up to 60-fold) stabilized against irreversible thermal denaturation*" (*see* abstract). Similarly, in the result and discussion section at page 1366, the authors conclude that "*all three reported strategies for preventing the dissociation of VL and VH lead to Fv molecules with dramatically improved thermal stabilities with the disulfide-linked mutants giving the most pronounced improvement.*" The authors further publicize the therapeutic and diagnostic significance of these three strategies and state that "*the reported strategies for generating Fv-fragments with improved physicochemical properties may extend their usefulness in biotechnology as well as in therapeutic and diagnostic applications*" *See* abstract, and the last sentence of the result/discussion section at page 1366.

As such, Glockshuber *et al.* does not provide any reason or motivation for one of ordinary skilled in the art to design alternative and better antigen-binding units having the characteristics of the instant invention. In fact, Glockshuber's conceptual framework of the three stabilization strategies has dominated the field for many years. Based on the reported success and three different workable strategies, one skilled in the art would not have looked to Glockshuber *et al.* for any suggestion to devise alternative and improved antigen-binding units, and certainly not the novel design by the Applicants that employs unique heterodimerization sequences to bring together and stabilize the VH and VL domains. While Applicants have

recognized and pointed out certain intrinsic limitations of the conventional methodologies, Glockshuber *et al.* do not suggest these limitations and hence the need for searching any other means to stabilize the VH and VL domains. Furthermore, nowhere in Glockshuber teaches or even suggests the use of heterodimerization sequences of any kind, let alone the type of heterodimerization sequence that lacks essentially the propensity to form a homodimer under physiological buffer conditions and/or at physiological body temperatures in order to create novel antigen-binding units.

In sum, Glockshuber in no way provides the requisite motivation to combine with any of the cited secondary references.

Pack *et al.* does not suggest the creation of new antigen-binding unit by stabilizing VH and VL regions; nor does it suggest the use of heterodimerization sequences for such application.

In the Final Office Action, the Office has also contended that the secondary reference by Pack *et al.* "*clearly teaches heterodimers for stabilizing the scFv molecules which bind antigen and bring binding domains together to form a bifunctional molecule. Thus, it would have been obvious to bring the VH and the VL domains of an antibody together with a heterodimerization domain as taught by Pack because of the inferiority of the methods to stabilize the molecules of Glockshuber.....*"

Applicants respectfully disagree with the Office's characterization. Pack *et al.* does not teach stabilization of the VH and VL domains to form scFv fragment; nor does it teach the use of heterodimerization sequences for such purpose. Pack et al., working in the same group of Glockshuber, followed the same conceptual framework that was established by Glockshuber previously. The purpose of Pack's research was to group together two scFv fragments pre-formed according to Glockshuber's method in order to reconstitute a bivalent, Y-shaped immunoglobulin-like molecule (*see* Figure 1). In other words, the objective of Pack *et al.* was to increase "avidity" of the molecule by stringing two pre-formed scFv together (*see* introduction at page 1579). Pack *et al.* achieved such objective by utilizing a homodimerization sequence (*see* Figure 1) and not heterodimerization sequence.

By contrary, the claimed invention concerns stabilizing the VH and VL domains to create a new antigen-binding unit. The strategy is entirely distinct from the conventional framework established by Glockshuber. Moreover, the invention utilizes heterodimerization sequences to pair and stabilize the VH and VL regions and thereby generating a novel antigen-binding unit. Both the concept of creating a new antigen-binding unit, and the specific application of the heterodimerization sequences are missing in Pack *et al.* Therefore, even if Pack *et al.* were to be combined with Glockshuber, the combined teachings do not add up to all of the limitations of the claimed invention. Given the entirely different objective of Pack *et al.*, it is not surprising that Pack *et al.* does not suggest generating novel antigen-binding units exhibiting the claimed characteristics. Consequently, Pack *et al.* does not compensate for the deficiencies of the primary reference by Glockshuber *et al.*

The other secondary references by Arndt *et al.*, Queen et al (U.S. Patent 5,693,762), and Kammerer et al also do not compensate for the deficiencies of Glockshuber *et al.*

The Arndt reference describes generating peptide libraries for selection of heterodimerization peptides based on the *fos* and *jun* leucine zippers. At the outset, this article is of little relevance with respect to antibody engineering, and does not pertain to design of novel antigen-binding units. While Arndt's in vivo selection system is capable of identifying heterodimerization peptides, the system is incapable of screening against those heterodimerization sequences still capable of forming homodimers under physiological buffer conditions and/or at physiological body temperatures. As noted above, claim 1 requires that "*at least one of the heterodimerization polypeptides is essentially incapable of forming a homodimer under physiological buffer conditions and/or at physiological body temperatures*."

In fact, Arndt *et al.* acknowledges this and other related intrinsic drawbacks of the selection system. Specifically, Arndt *et al.* states at page 629 the following:

> **"[The reported results] led us to conclude that we had indeed selected heterodimeric coiled coils. However, this still remains to be proven by biophysical analysis of the dominant pair, WinZip-A1B1. Furthermore, we were still lacking information on whether the selection system was able to not only select for stability but also for heterospecificity."**

Arndt *et al.* further reports that the best pair of coiled-coil peptides, namely WinZip-A1 and WinZip-B1 selected by the system, still exhibit homodimerization propensity under physiological buffer conditions and/or at physiological body temperatures. *See* results at page 633 and figure 5(b). Therefore, Arndt does not teach a necessary limitation of claim 1.

The Queen reference discloses a method of humanizing immunoglobulins. However, it does not describe or even suggest an approach to enable the stabilization of VL and VH regions for creating an antigen-binding unit. In fact, the Queen reference does not even pertain to construction of antigen-binding unit. Rather, it focuses on modifying the existing immunoglobulins in order to make the whole immunoglobulin less immunogenic in humans. Given the entirely different objectives of the Queen reference, it is not surprising that nothing in this reference provides even a hint of the claimed subject matter.

Finally, the reliance of Kammerer reference would require improper hindsight reasoning. This is a reference disclosed and discussed in the instant application (*see* paragraph 201). As detailed in the specification, Kammerer *et al.* concerns the characterization of the $GABA_B$-R1 and $GABA_B$-R2 coiled-coil sequences. It does not teach or suggest the specific use of these unique heterodimerization sequences for constructing antigen-binding units. Kammerer's experiments were directed to analyzing the biochemical properties of these sequences. Consequently, there is nothing in Kammerer that suggests using the $GABA_B$ heterodimerization sequences to stabilize the VL and VH regions. In fact, the Kammerer reference does not even pertain to antibody engineering. Only with hindsight knowledge of the present invention could one think of Kammerer *et al.* as a source of motivation to come up the claimed antigen-binding units.

For the reasons stated above and previously, Appellants submit that: (i) the primary reference by Glockshuber does not provide the requisite motivation for one of ordinary skill in the art to search for alternative design of antigen-binding units as instantly claimed; and (ii) the

secondary references of Pack, Arndt and Queen, alone or in any combinations, do not ~~provid~~ compensate for the deficiencies of the primary reference; and (iii) invocation of the Kammerer reference would require improper hindsight reasoning. Accordingly, Appellants respectfully submit that the Office has not established a *prima facie* case of obviousness of the claimed compositions of matter. This rejection should be withdrawn.

2. *Rejection under 35 U.S.C. § 112 ¶ 1*

Claim 94 is rejected under 35 U.S.C. 112, first paragraph, as allegedly reciting new matter. Specifically, the Office object to the recitation of the term "affinity."

Claim 94 as amended now recite "capability", thereby obviating this rejection. The term "capability" finds literal support in the title of Figure 11B and the figure legend in paragraph 52. Applicants submit that this amendment does not narrow the originally presented claim in any way. The amendment is introduced merely to comport with the literal written description in the corresponding portions of the specification. The apparent binding capability as specified in claim 94 may reflect, in part or in whole, the binding affinity of the claimed antigen-binding unit. Thus, Applicants assert that the claim as amended is entitled to the same doctrine of equivalents treatment that would have been available for the originally presented claim. Withdrawal of this rejection is respectfully requested.

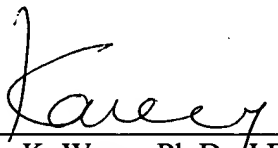
III. CONCLUSION

Applicants believe that this amendment has fully addressed all of the issues raised by the Examiner. In view of the claim amendments and remarks to the rejections, Applicants believe that this application is in condition of allowance. Upon allowance of the pending claims 1-30 and 87-94, the Examiner is authorized to cancel claims 31-86 drawn to nonelected subject matters. An early Notice of Allowance is earnestly requested.

No extension fee is required for filing this amendment. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from the Deposit Account No. **08-3038** of Howrey Simon Arnold & White, LLP with a reference to Docket No. **13403.004.NPUS00**.

Date: March 30, 2004

Respectfully submitted,



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